UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,438	11/14/2001	David Botstein	10466/201	2374

35489 7590 10/24/2007

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
10/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/990,438	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,125 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124,125 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Withdrawal of Finality

In view of the Appeal Brief filed on 7/19/07, PROSECUTION IS HEREBY REOPENED. A reinstated grounds of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Claim Rejections - 35 USC §§ 101 and 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 124-125 and 129-131 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action.

Claims 124-125 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth here, one skilled in the art clearly would not know how to use the claimed invention.

A portion of the previous rejection is withdrawn. Specifically the Examiner no longer asserts that mRNA levels do not generally correlate with protein levels. Therefore, the following references are no longer being relied upon to support the rejections: Chen et al., Lian et al., Hu et al., Haynes et al., Fessler et al. and Gygi et al. However, the rejection is maintained for the following reasons:

The claims are directed to isolated polypeptides comprising an amino acid of SEQ ID NO: 33, also known as PRO290, or the amino acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 209790. It is noted that the specification asserts several utilities for the claimed polypeptides other than as a marker for lung or colon tumors, all of which have been found to be non-specific and/or insubstantial. For discussion of these utilities, see Office Action mailed 19 October 2005. However, these asserted utilities will not be readdressed here due to Applicants' indication that they are relying upon the gene amplification assay for utility and enablement.

At pages 539-555, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO290 had a ΔCt value of at least 1.22-2.07 for 5/19 lung tumor samples and 1.16 and 1.56 for 2/17 colon tumor samples. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 545, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." At page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.22), and (b) that very few values were obtained that were at least 2.

While these data are pertinent to utility and enablement of PRO290 *genomic DNA* for use in lung or colon tumor diagnosis, the data do not directly bear on the utility of the claimed PRO290 *polypeptides*. It is noted that the amplification in lung or colon tumors of the nucleic acid encoding the PRO299 polypeptide is not an activity of the polypeptide, but rather a characteristic of a nucleic acid. In order for PRO290 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and, subsequently, increased polypeptide levels. No data regarding PRO290 mRNA or PRO290 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, Pennica et al. (1998, PNAS USA 95:14717-14722, previously of record), disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." (p. 14722, second paragraph of left column)

Additional details are provided in the section entitled, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors" on pp. 14720-14721. See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052, previously of record), who state in the abstract that, "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template."

Godbout et al. (J. Biol. Chem 273(33):21161, 1998, cited by Examiner 10/18/06) teaches in the abstract that, "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by

the DDX gene had been characterized as being a putative RNA helicase, a type of enzyme that would be expected to confer a selective advantage to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state:

> It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell (48, 49)." For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons.

On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO290 gene. It is not disclosed, and based upon the sequence searches in this case the Examiner can not find any reason to suspect, that the protein encoded by the PRO290 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Therefore, one of skill in the art would *not* expect PRO290 overexpression even if the genomic DNA is amplified. Further, it could not be determined whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO290.

An additional reference that provides evidence that gene amplification does not necessarily lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006 (cited by Examiner 10/18/06). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, paragraph beginning at the bottom of col. 1, Li et al. state:

> Although the main focus of this study was to specifically identify putative oncogenes, it should be noted that 90.7% of the genes showing high protein expression did not show corresponding increases in both DNA copy number and transcript, a finding consistent with that of others that transcriptional, translational, and post-translational regulatory mechanisms can greately influence

> the abundance of portein in lung tumorigenesis (Chen *et al.*, 2002).... In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but lack biological relevance in terms of the development of lung adenocarcinoma.

The findings of Li et al. are that over half of the genes which were amplified were not overexpressed at the mRNA level. These findings show one cannot reasonably conclude that genomic amplification correlates with elevated mRNA levels.

While the Examiner has the resources to cite only a handful of references showing the unpredictability of a correlation between genomic DNA and protein levels, these references stand to show that one cannot make assumptions about the use of PRO290 polypeptide in view of the methods used and information provided in the instant specification. Data pertaining to PRO290 genomic DNA do not indicate anything significant regarding the claimed PRO290 polypeptides. Neither the data nor the art support the specification's assertion that PRO290 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO290 polypeptide is overexpressed in any cancer to the extent that it could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO290 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO290 *polypeptides* as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Godbout et al., and Li et al., all of which are of record and have been previously discussed), the rejections are proper.

Applicants arguments directed to the references of Lian et al., Fessler et al., Chen et al., Hu et al., Haynes et al. and Gygi et al. will not be addressed since they are no longer considered relevant to the rejection at hand.

Applicants argue (p. 4) that the Examiner has failed to distinguish between the microarray assay for determining mRNA expression and amplification assay for determining genomic DNA amplification. The argument has been fully considered, but is not persuasive. The references of Pennica et al., Konopka et al., Li et al and Godbout et al., among other previous cited, distinguish the assays and are relevant to the issue of gene amplification compared to mRNA expression.

Applicants argue (p. 4) that a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal NO. 2006-1469) acknowledged that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." Because Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides (see Appeal Brief filed 7/19/07, p. 4, beginning of arguments), and the Examiner no longer contests the general correlation between mRNA and protein levels for a particular protein, this Board decision is not pertinent to the instant case.

At pages 4-5 and the paragraph bridging pages 10-11 of Applicants' Brief, it is argued that the data in Example 170 (starting at p. 539 of the specification) describes results of a gene amplification assay. Applicants characterize the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Applicants report that the gene encoding PRO290 was significantly amplified (2.297-fold to 4.2-fold) in 5/19 lung tumors. This has been fully considered but is not found to be persuasive. First, it is important to note that the gene encoding PRO290 was found not to be amplified in 14 out of nineteen lung tumors (6/11 SqCCa-

type tumors) and 15/17 colon tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 547). The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy (see, *e.g.,* Sen et al. and Hittelman et al.). Given these details, one skilled in the art would not conclude that the gene encoding PRO290 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA or polypeptide levels (see Pennica et al., Konopka et al., Godbout et al. and Li et al.).

On the top of p. 5 and bottom of p. 11, Applicants refer to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 02 August 2005, as a copy from different case (09/903,925). Applicants quote from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Applicants conclude that one skilled in the art would consider the 2.297-fold to 4.2-fold amplification of the gene encoding PRO290 in 5 lung tumors significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.297- to 4.2-fold amplification of the gene encoding PRO290 in five lung tumors is significant and credible. Credibility has never been questioned. However, the significance can be questioned since 14 out of nineteen lung tumor (6/11 SqCCa-type tumors) and 15/17 colon tumor samples did *not* show an amplification of the gene encoding PRO290, and the control used was not a matched non-tumor lung or colon sample, respectively,

but rather was a pooled DNA sample from blood of healthy subjects. As discussed above, the art uses matched tissue samples. Pennica et al., Konopka et al., Sen et al., Hittelman et al., Godbout et al. and Li et al. speak to the strength of the opposing evidence as discussed in the previous Office and in the rejection above. The expert has interest in the outcome of the case since Dr. Goddard is listed as an inventor and is employed by the assignee. Finally, the expert refers to three publications as factual support for the conclusions in the declaration. However, neither Livak et al. nor Heid et al. appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica et al. was found to support the rejection, as discussed above. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins thereof are found at increased levels in cancerous tissues. Since the claims under examination are direct to polypeptide not genes, this question is critical. Based on consideration of the evidence as a whole, the rejection is proper.

Applicants argue (p. 5, top of p. 12 and paragraph bridging pages 20-21) that ample evidence has been provided to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded polypeptide is also expressed at an elevated level. Applicants refer to Orntoft et al., Hyman et al. and Pollack et al. as teaching that, in general, gene amplification increases mRNA expression. Applicants point to the Polakis declarations (submitted under 37 C.F.R. § 1.132 on 07/31/2006 and 8/20/2004) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Applicants urge that even if there were no correlation between gene amplification and mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer still has a patentable utility in that it yields a more accurate tumor classification, relying upon the declaration by Dr. Ashkenzi (submitted under 37 C.F.R. § 1.132 on 08/20/04) and the "real world" example of breast cancer marker HER-2/neu of Hanna et al. reference. Finally, Applicants conclude that there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO290 conveys utility to the claimed PRO290 polypeptides. This has been fully considered but is not found to be persuasive. Orntoft et al. looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region (see for example, p 44, last paragraph of col. 1).

Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with clusters of chromosomal material containing strong gains, but it is not known whether PRO290 is in a gene cluster in a region of a chromosome that is highly amplified. They go on to say that detection was very limited. Further, the data do not look at a 1:1 correspondence of genomic DNA and the mRNA which is transcribed from it. It looked at gene clusters in chromosomal regions. Therefore, the results of Orntoft et al. are not directly applicable to the instant situation for PRO290. Hyman et al. used the same CGH approach in their research. Less than half (44%) of *highly* amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability.

The Polakis declarations are directed to the argument that mRNA levels are predictive of protein levels and that PRO290 mRNA is significantly overexpressed in tumor compared to a normal control. Again, the issue at hand is not the correlation of mRNA to protein level but of genomic DNA copy number to mRNA or encoded protein. Only Dr. Polakis' conclusions are provided in the declarations. The first and second declarations of Dr. Polakis were considered, as were the quoted statements' relationship to relevant art. While the opinions of Dr. Polakis have been considered, they are not found persuasive to overcome the rejection of the claimed invention under 35 USC 101 or 112, first paragraph, enablement for the reasons of record and for the reasons that they do not address the correspondence of genomic DNA levels to protein levels.

The Hanna et al. reference actually supports the rejection, since Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level

of polypeptide expression must be tested empirically. The specification does not provide this further information about polypeptide expression, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

In the declaration, Dr. Ashkenazi states that, even when amplification of a cancer marker gene does not result in significant overexpression of the corresponding gene product, the absence of gene product overexpression still provides significant information for cancer diagnosis and treatment. Applicants also refer to Hanna et al., previous cited, in which breast cancer diagnosis includes testing for HER-2/neu amplification and absence of HER-2/neu gene product overexpression. Applicants argue that such information leads to a more accurate classification of the cancer and a more effective way of treating it. Applicants argue that the PRO290 polypeptide is also useful in tumor categorization (such as suggested by the Ashkenazi declaration and the Hanna et al. reference), the results of which become an important tool in the hands of a physician enabling the selection of treatment modality that holds the most promise for the successful treatment of a patient. This has been fully considered but is not found to be persuasive. While it may be true that lack of overexpression of a gene product can also provide useful information in tumor categorization, the specification does not disclose such further testing of PRO290 gene product expression levels. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form. Furthermore, the specification provides no assertion that the claimed PRO290 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO290. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial. Finally, Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. Hanna et al. say these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that

"In general, FISH [gene] and IHC[protein] results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." Therefore, the issues of Her-2 cannot be generalized to any gene expressed in a tumor. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments to reasonably confirm the real world context of the asserted utility. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Applicants argue (pages 6 and 17) that even if amplification of the PRO290 gene were due to aneuploidy, the art exemplified by Hittelman et al. supports the PRO290 gene as a "useful marker for precancerous cells or damaged tissue that could later develop into cancer." This has been fully considered but is not found to be persuasive. This is especially key for lung, since the art shows that both cancerous and noncancerous lung tissue can be aneuploidy (see Sen et al. and Hittelman et al.). Given these details, one skilled in the art would not conclude that the gene encoding PRO290 would be useful as a cancer or precancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Further, because it is the PRO290 polypeptide and not the gene which is claimed, even if the reported amplification of the nucleic acid of SEQ ID NO:32 were due to aneuploidy, this does not support a diagnostic utility for the encoded polypeptide or antibody for the reasons previously discussed.

At pages 6 and 21 of the Brief, Applicants note that the sale of gene expression chips to measure mRNA levels is a highly successful business. Applicants conclude that the research community believes that the information obtained from the chips is useful (*i.e.*, that it is more likely than not that the results are informative for protein levels). This has been fully considered but is not found to be persuasive. Evidence of commercial success has no bearing on the issue of utility. The research community could just as easily be interested in the gene chips as a way of providing preliminary results, which would then be followed up with actual testing of protein levels.

Applicants argue (p. 8) "that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use." This statement relates to the Court's decision in *Nelson v. Bowler*. In that decision, the CCPA

says that specific therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. However, in this instance, pharmacological activity is not the same as gene amplification. In *Nelson,* the court held that the compound of which utility was in question, was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson,* the instant application does not have a showing of practical utility. There are no test results to correlate the presence of PRO290 polypeptide with a diagnostic for lung or colon cancer. It is maintained that the instant application has not established the use of a polypeptide of SEQ ID NO:33 and utility as a cancer diagnostic. A finding of amplification of the genomic nucleic acid of SEQ ID NO:32 cannot be assumed to correlate to the higher expression of the encoded polypeptide in the same tissues.

On page 8, Applicants also cite *Cross v. Iizuka* (Fed. Cir. 1985), arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* amplification data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is whether genomic DNA levels correlated with encoded protein levels.

Applicants take issue (pages 12-13) with the Pennica et al. and Konopka et al. references relied upon by the Examiner. Specifically, Applicants characterize Pennica et al. as being limited to WISP genes, and does not speak to the correlation of gene amplification and protein expression for genes in general. Applicants point out that there was such a correlation for WISP-1 as disclosed by Pennica et al. Applicants characterize Konopka et al. as being limited to the *abl* gene, and not speaking to genes in general. Applicants conclude that the Examiner must show evidence that it is more likely than not that the correlation does not exist, and that a *prima facie* case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general because they show a lack of correlation between gene amplification and gene product overexpression. The instant case also concerns a single gene. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al.

The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.) and (2) no evidence has been brought forth regarding levels of PRO290 mRNA levels or PRO290 polypeptide levels in cancerous tissue. Finally, Pennica et al. provide evidence that closely related WISP genes show unpredictable gene amplification, mRNA and polypeptide levels. As discussed in the rejections above, these references are pertinent to the lack of reasonable expectation that for any given gene the level of gene copy number will correlate with protein expression.

Applicants argue (pages 16-17) that Sen et al. supports the position that aneuploidy can be used to diagnose cancerous and precancerous tissue, as well as a means of risk assessment and prognosis. The argument has been fully considered, but is not persuasive. As discussed above, aneuploidy can occur in noncancerous tissues, for example, in the lung where the art shows that both cancerous and noncancerous lung tissue can be aneuploidy (see Sen et al. and Hittelman et al.). Also in contrast to the art (*e.g.*, see Pennica et al., Konopka et al.), matched tissue samples were not used for controls in determining gene copy number in the instant application. Rather, the control DNA appears to have been isolated from blood (bottom of p. 547). Given these details, one skilled in the art would not conclude that the gene encoding PRO290 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as very preliminary. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA or polypeptide levels in many cases (see Pennica et al., Konopka et al., Godbout et al. and Li et al.).

Applicants argue (paragraph bridging pages 17-18) that Bea et al. supports "Applicants' assertion that gene amplification is correlated with both increased mRNA and protein expression." The argument has been fully considered, but is not persuasive. There are two points to be made. First, while Bea et al. found (p. 2411, end of col. 2) that 4/36 MCL tumors showed both high BM1-1 gene amplification and mRNA levels, they also found that, "In addition, five MCLs with no structural alterations in the gene showed high mRNA levels similar to those observed in tumors with BM1-1 gene amplification, suggesting that other mechanisms may be involved in up-regulation of the gene in these lymphomas." They conclude (p. 2411, col. 2, end of first full paragraph), "Although we found no evidence for BM1-1 gene rearrangements

or amplifications in a substantial set of carcinomas, this does not exclude the possibility of increased gene expression or protein levels in these tumors." Bea et al. serve to show that increased mRNA or protein expression does not necessarily correlate with gene amplification. Because the data set for gene amplification is so small, only 11% of the tested MCLs, and only one particular type of cell was able to be examined for gene amplification, one cannot draw general conclusions about a relationship between gene amplification and mRNA or protein expression. Second, it is not unexpected that BM1-1 as a putative oncogene, which seems to participate in cell cycle regulation and senescence, when amplified in the genome would also be amplified as mRNA and have correspondingly increased protein expression. PRO290 is not a putative oncogene, and the function of the encoded protein is not known.

Applicants argue (p. 18) that PRO290 was never claimed to be similar to DDX1 of Godbout et al., nor that it was an RNA helicase or confers a selective advantage to cell survival. However, Godbout shows a good correlation between protein levels and genomic DNA amplification. Structure/function data is not a requirement for the utility requirement. The argument has been fully considered, but is not persuasive. Applicants have missed the point of Godbout et al., which is that only those genes which confer a selective advantage to cell survival, for example a RNA helicase (though there are many other types of genes which could confer a selective advantage), would reasonably be expected to be amplified. The Examiner cannot find any reason to suspect that the protein encoded by the PRO290 gene would confer any selective advantage on a cell expressing it. On page 21167, right column, first full paragraph, Godbout et al. state, "It is generally accepted that co-amplified genes are not overexpressed unless they provide a selective growth advantage to the cell (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." There is no evidence in the instant application that PRO290 confers any growth advantage to a cell, and thus it cannot be presumed that the

mRNA or protein is overexpressed even if the genomic DNA including the gene being studied is amplified. Godbout et al. support the unpredictability that for any particular amplified genomic DNA, the corresponding mRNA or protein will be overexpressed.

Applicants argue that Li et al. acknowledge their results differed from those of Hyman et al. and Pollack et al. (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression", with Li et al. noting the difference may be from different methods used to study breast cancer and lung adenocarcinoma. Li et al. used a lower fold amplification threshold (1.4 compared to 2.0 in the instant application). The argument has been fully considered, but is not persuasive. Even if Li et al. used a lower amplification threshold, they showed that a *significant majority* of genes that are amplified do not have overexpressed mRNA (p. 2633, col. 2, end of first paragraph):

> In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but lack biological relevance in terms of the development of lung adenocarcinoma.

Similarly, Hyman et al. found less than half (44%) of *highly* amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Like Hyman et al., Pollack et al. concentrated on large chromosome regions showing *high* amplification (p. 12965). Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability for any particular gene. Both Li et al. and Hyman et al. show that less than half of the genes showing amplified DNA also showed elevated expression of mRNA. These references in combination with other references such as Godbout et al., Pennica et al. and Konopka et al. support a conclusion that one of skill in the art would not reasonably expect that for any particular amplified gene the corresponding mRNA or protein will also be overexpressed. The art of record does **not** support Applicants' statement (bottom of p. 19) that "increased genes/transcripts levels mostly correlated with increased protein levels, even if accurate predication of proteins could not be made."

Applicants argue (page 20) that the declarations by Dr. Polakis are pertinent to the instant rejection and are based on factual findings. The declarations support the argument that mRNA levels are predictive of protein levels and that PRO290 mRNA is significantly overexpressed in tumor compared to a normal control. The argument has been fully considered, but is not persuasive. Again, the issue at hand is not the correlation of mRNA to protein level but of genomic DNA copy number. The first and second declarations of Dr. Polakis were considered, as were the quoted statements' relationship to relevant art. While the opinions of Dr. Polakis have been considered, they are not found persuasive to overcome the rejection of the claimed invention under 35 USC 101 or 112, first paragraph, enablement for the reasons of record and for the reasons that they do not address the correspondence of genomic DNA levels to protein levels.

Conclusion

All claims are drawn to the same invention claimed in the application and could have been finally rejected on the grounds and art of record in the next Office action. The new rejection is a reinstatement of a previous rejection (*e.g.*, 5/13/06, 10/19/05) that was inadvertently omitted in the previous Office action and was previously responded to by Applicants (7/31/06). No new art has been cited. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873.

Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

October 22, 2007

LORRAINE SPECTOR
PRIMARY EXAMINER